

What is claimed is:

1. A compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding HIF1 $\alpha$ , wherein said compound specifically hybridizes with said nucleic acid molecule encoding HIF1 $\alpha$  and inhibits the expression of HIF1 $\alpha$ .

2. The compound of claim 1 comprising 12 to 50 nucleobases in length.

3. The compound of claim 2 comprising 15 to 30 nucleobases in length.

4. The compound of claim 1 comprising an oligonucleotide.

5. The compound of claim 4 comprising an antisense oligonucleotide.

6. The compound of claim 4 comprising a DNA oligonucleotide.

7. The compound of claim 4 comprising an RNA oligonucleotide.

8. The compound of claim 4 comprising a chimeric oligonucleotide.

9. The compound of claim 4 wherein at least a portion of said compound hybridizes with RNA to form an oligonucleotide-RNA duplex.

10. The compound of claim 1 having at least 70% complementarity with a nucleic acid molecule encoding HIF1 $\alpha$  (SEQ ID NO: 4) said compound specifically hybridizing to and inhibiting the expression of HIF1 $\alpha$ .

11. The compound of claim 1 having at least 80% complementarity with a nucleic acid molecule encoding HIF1 $\alpha$  (SEQ ID NO: 4) said compound specifically hybridizing to and inhibiting the expression of HIF1 $\alpha$ .

12. The compound of claim 1 having at least 90% complementarity with a nucleic acid molecule encoding HIF1 $\alpha$  (SEQ ID NO: 4) said compound specifically hybridizing to and inhibiting the expression of HIF1 $\alpha$ .

13. The compound of claim 1 having at least 95% complementarity with a nucleic acid molecule encoding HIF1 $\alpha$  (SEQ ID NO: 4) said compound specifically hybridizing to and inhibiting the expression of HIF1 $\alpha$ .

14. The compound of claim 1 having at least 70% complementarity with a nucleic acid molecule encoding HIF1 $\alpha$  (SEQ ID NO: 133) said compound specifically hybridizing to and inhibiting the expression of HIF1 $\alpha$ .

15. The compound of claim 1 having at least 80% complementarity with a nucleic acid molecule encoding HIF1 $\alpha$  (SEQ ID NO: 133) said compound specifically hybridizing to and inhibiting the expression of HIF1 $\alpha$ .

16. The compound of claim 1 having at least 90% complementarity with a nucleic acid molecule encoding HIF1 $\alpha$  (SEQ ID NO: 133) said compound specifically hybridizing to and inhibiting the expression of HIF1 $\alpha$ .

17. The compound of claim 1 having at least 95% complementarity with a nucleic acid molecule encoding HIF1 $\alpha$  (SEQ ID NO: 133) said compound specifically hybridizing to and inhibiting the expression of HIF1 $\alpha$ .

18. The compound of claim 1 having at least 70% complementarity with a nucleic acid molecule encoding HIF1 $\alpha$  (SEQ ID NO: 206) said compound specifically hybridizing to and inhibiting the expression of HIF1 $\alpha$ .

19. The compound of claim 1 having at least 80% complementarity with a nucleic acid molecule encoding HIF1 $\alpha$  (SEQ ID NO: 206) said compound specifically hybridizing to and inhibiting the expression of HIF1 $\alpha$ .

20. The compound of claim 1 having at least 90% complementarity with a nucleic acid molecule encoding HIF1 $\alpha$  (SEQ ID NO: 206) said compound specifically hybridizing to and inhibiting the expression of HIF1 $\alpha$ .

21. The compound of claim 1 having at least 95% complementarity with a nucleic acid molecule encoding HIF1 $\alpha$  (SEQ ID NO: 206) said compound specifically hybridizing to and inhibiting the expression of HIF1 $\alpha$ .

22. The compound of claim 1 having at least one modified internucleoside linkage, sugar moiety, or nucleobase.

23. The compound of claim 1 having at least one 2'-O-methoxyethyl sugar moiety.

24. The compound of claim 1 having at least one phosphorothioate internucleoside linkage.

25. The compound of claim 1 having at least one 5-methylcytosine.

26. The compound of claim 1 comprising at least an 8-nucleobase portion of SEQ ID NO: SEQ ID NOS 14, 15, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 28, 29, 30, 31, 32, 35, 36, 40, 41, 42, 43, 44, 45, 47, 48, 49, 50, 51, 53, 55, 57, 58, 59, 60, 61, 63, 64, 66, 67, 69, 70, 71, 74, 75, 78, 83, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 166, 167, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 192, 193, 194, 197, 198, 200, 201, 202, 203 or 207.

27. The compound of claim 1 having a sequence selected from the group consisting of SEQ ID NO: SEQ ID NOS 14, 15, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 28, 29, 30, 31, 32, 35, 36, 40, 41, 42, 43, 44, 45, 47, 48, 49, 50, 51, 53, 55, 57, 58, 59, 60, 61, 63, 64, 66, 67, 69, 70, 71, 74, 75, 78,

83, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 166, 167, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 192, 193, 194, 197, 198, 200, 201, 202, 203 and 207.

28. The compound of claim 1, wherein said compound comprises an antisense nucleic acid molecule that is specifically hybridizable with a 5'-untranslated region (5'UTR) of hypoxia-inducible factor 1 alpha (SEQ ID NO: 4).

29. The compound of claim 1, wherein said compound comprises an antisense nucleic acid molecule that is specifically hybridizable with a start region of hypoxia-inducible factor 1 alpha (SEQ ID NO: 4).

30. The compound of claim 1, wherein said compound comprises an antisense nucleic acid molecule that is specifically hybridizable with a coding region of hypoxia-inducible factor 1 alpha (SEQ ID NO: 4).

31. The compound of claim 1, wherein said compound comprises an antisense nucleic acid molecule that is specifically hybridizable with a stop region of hypoxia-inducible factor 1 alpha (SEQ ID NO: 4).

32. The compound of claim 1, wherein said compound comprises an antisense nucleic acid molecule that is specifically hybridizable with a 3'-untranslated region of hypoxia-inducible factor 1 alpha (SEQ ID NO: 4).

33. A method of inhibiting the expression of HIF1 $\alpha$  in cells or tissues comprising contacting said cells or tissues with the compound of claim 1 so that expression of HIF1 $\alpha$  is inhibited.

34. A method of screening for a modulator of HIF1 $\alpha$ , the method comprising the steps of:

a. contacting a preferred target segment of a nucleic acid molecule encoding HIF1 $\alpha$  with one or more candidate modulators of HIF1 $\alpha$ , and

b. identifying one or more modulators of HIF1 $\alpha$  expression which modulate the expression of HIF1 $\alpha$ .

35. The method of claim 19 wherein the modulator of HIF1 $\alpha$  expression comprises an oligonucleotide, an antisense oligonucleotide, a DNA oligonucleotide, an RNA oligonucleotide, an RNA oligonucleotide having at least a portion of said RNA oligonucleotide capable of hybridizing with RNA to form an oligonucleotide-RNA duplex, or a chimeric oligonucleotide.

36. A diagnostic method for identifying a disease state comprising identifying the presence of HIF1 $\alpha$  in a sample using at least one of the primers comprising SEQ ID NOs 5 or 6, or the probe comprising SEQ ID NO: 7.

37. A kit or assay device comprising the compound of claim 1.

38. A method of treating an animal having a disease or condition associated with HIF1 $\alpha$  comprising administering to said animal a therapeutically or prophylactically effective amount of the compound of claim 1 so that expression of HIF1 $\alpha$  is inhibited.

39. The method of claim 38 wherein the disease or condition is a hyperproliferative disorder.

40. The method of claim 39 wherein the hyperproliferative disorder is cancer.

41. The method of claim 40 wherein the cancer carries a p53 mutation.

42. The method of claim 39 wherein the hyperproliferative disorder is an angiogenic disorder.

43. The method of claim 42 wherein the angiogenic disorder affects the eye.

44. A composition comprising the compound of claim 1 in a pharmaceutically acceptable carrier.

45. A compound of claim 1 which also inhibits the expression of HIF2 $\alpha$ .

46. A composition comprising a compound of claim 45 in a pharmaceutically acceptable carrier.

47. A compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding HIF2 $\alpha$ , wherein said compound specifically hybridizes with said nucleic acid molecule encoding HIF2 $\alpha$  and inhibits the expression of HIF2 $\alpha$ .

48. The compound of claim 47 comprising 12 to 50 nucleobases in length.

49. The compound of claim 48 comprising 15 to 30 nucleobases in length.

50. The compound of claim 47 comprising an oligonucleotide.

51. The compound of claim 50 comprising an antisense oligonucleotide.

52. The compound of claim 50 comprising a DNA oligonucleotide.

53. The compound of claim 50 comprising an RNA oligonucleotide.

54. The compound of claim 50 comprising a chimeric oligonucleotide.

55. The compound of claim 50 wherein at least a portion of said compound hybridizes with RNA to form an oligonucleotide-RNA duplex.

56. The compound of claim 47 having at least 70% complementarity with a nucleic acid molecule encoding HIF2 $\alpha$  (SEQ ID NO: 208) said compound specifically hybridizing to and inhibiting the expression of HIF2 $\alpha$ .

57. The compound of claim 47 having at least 80% complementarity with a nucleic acid molecule encoding HIF2 $\alpha$  (SEQ ID NO: 208) said compound specifically hybridizing to and inhibiting the expression of HIF2 $\alpha$ .

58. The compound of claim 47 having at least 90% complementarity with a nucleic acid molecule encoding HIF2 $\alpha$  (SEQ ID NO: 208) said compound specifically hybridizing to and inhibiting the expression of HIF2 $\alpha$ .

59. The compound of claim 47 having at least 95% complementarity with a nucleic acid molecule encoding HIF2 $\alpha$  (SEQ ID NO: 208) said compound specifically hybridizing to and inhibiting the expression of HIF2 $\alpha$ .

60. The compound of claim 47 having at least 70% complementarity with a nucleic acid molecule encoding HIF2 $\alpha$  (SEQ ID NO: 212) said compound specifically hybridizing to and inhibiting the expression of HIF2 $\alpha$ .

61. The compound of claim 47 having at least 80% complementarity with a nucleic acid molecule encoding HIF2 $\alpha$  (SEQ ID NO: 212) said compound specifically hybridizing to and inhibiting the expression of HIF2 $\alpha$ .

62. The compound of claim 47 having at least 90% complementarity with a nucleic acid molecule encoding HIF2 $\alpha$  (SEQ ID NO: 212) said compound specifically hybridizing to and inhibiting the expression of HIF2 $\alpha$ .

63. The compound of claim 47 having at least 95% complementarity with a nucleic acid molecule encoding HIF2 $\alpha$  (SEQ ID NO: 212) said compound specifically hybridizing to and inhibiting the expression of HIF2 $\alpha$ .

64. The compound of claim 47 having at least one modified internucleoside linkage, sugar moiety, or nucleobase.

65. The compound of claim 47 having at least one 2'-O-methoxyethyl sugar moiety.

66. The compound of claim 47 having at least one phosphorothioate internucleoside linkage.

67. The compound of claim 47 having at least one 5-methylcytosine.

68. The compound of claim 47 comprising at least an 8-nucleobase portion of SEQ ID NO: SEQ ID NOS 219, 220, 221, 211, 223, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254 or 255.

69. The compound of claim 47 having a sequence selected from the group consisting of SEQ ID NO: SEQ ID NOS 219, 220, 221, 211, 223, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254 and 255.

70. The compound of claim 47 comprising at least an 8-nucleobase portion of SEQ ID NO: 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 305, 306, 307, 308, 309, 310, 311, 313, 314, 315, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 331, 332, 333, 334 or 335.

71. The compound of claim 47 having a sequence selected from the group consisting of SEQ ID NO, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 305, 306, 307, 308, 309, 310, 311, 313, 314, 315, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 331, 332, 333, 334 and 335.

72. The compound of claim 47, wherein said compound comprises an antisense nucleic acid molecule that is specifically hybridizable with a 5'-untranslated region (5'UTR) of hypoxia-inducible factor 2 alpha (SEQ ID NO: 208).

73. The compound of claim 47, wherein said compound comprises an antisense nucleic acid molecule that is specifically hybridizable with a start region of hypoxia-inducible factor 2 alpha (SEQ ID NO: 208).



74. The compound of claim 47, wherein said compound comprises an antisense nucleic acid molecule that is specifically hybridizable with a coding region of hypoxia-inducible factor 2 alpha (SEQ ID NO: 208).

75. The compound of claim 47, wherein said compound comprises an antisense nucleic acid molecule that is specifically hybridizable with a stop region of hypoxia-inducible factor 2 alpha (SEQ ID NO: 208).

76. The compound of claim 47, wherein said compound comprises an antisense nucleic acid molecule that is specifically hybridizable with a 3'-untranslated region of hypoxia-inducible factor 2 alpha (SEQ ID NO: 208).

77. A method of inhibiting the expression of HIF2 $\alpha$  in cells or tissues comprising contacting said cells or tissues with the compound of claim 47 so that expression of HIF2 $\alpha$  is inhibited.

78. A method of screening for a modulator of HIF2 $\alpha$ , the method comprising the steps of:

a. contacting a preferred target segment of a nucleic acid molecule encoding HIF2 $\alpha$  with one or more candidate modulators of HIF2 $\alpha$ , and

b. identifying one or more modulators of HIF2 $\alpha$  expression which modulate the expression of HIF2 $\alpha$ .

79. The method of claim 78 wherein the modulator of HIF2 $\alpha$  expression comprises an oligonucleotide, an antisense oligonucleotide, a DNA oligonucleotide, an RNA oligonucleotide, an RNA oligonucleotide having at least a portion of said RNA oligonucleotide capable of hybridizing with RNA to form an oligonucleotide-RNA duplex, or a chimeric oligonucleotide.

80. A diagnostic method for identifying a disease state comprising identifying the presence of HIF2 $\alpha$  in a sample using at least one of the primers comprising SEQ ID NOs 209 or 210, or the probe comprising SEQ ID NO: 211.

81. A kit or assay device comprising the compound of claim 47.

82. A method of treating an animal having a disease or condition associated with HIF2 $\alpha$  comprising administering to said animal a therapeutically or prophylactically effective amount of the compound of claim 47 so that expression of HIF2 $\alpha$  is inhibited.

83. The method of claim 82 wherein the disease or condition is a hyperproliferative disorder.

84. The method of claim 83 wherein the hyperproliferative disorder is cancer.

85. The method of claim 84 wherein the cancer carries a p53 mutation.

86. The method of claim 83 wherein the hyperproliferative disorder is an angiogenic disorder.

87. The method of claim 86 wherein the angiogenic disorder affects the eye.

88. A composition comprising the compound of claim 47 in a pharmaceutically acceptable carrier.

89. A compound of claim 47 which also inhibits the expression of HIF1 $\alpha$ .

90. A composition comprising a compound of claim 89 in a pharmaceutically acceptable carrier.

91. An antisense compound which inhibits the expression of HIF1 $\alpha$  and HIF2 $\alpha$ .

92. The antisense compound of claim 91 comprising SEQ ID NO: 443, 444, 233, 141, 445, 446, 447, 448, 449 or 450.

93. The antisense compound of claim 91 which comprises at least one universal base.

94. The antisense compound of claim 93 wherein the universal base is inosine or 3-nitropyrrole.

95. A composition comprising the compound of claim 91 and a pharmaceutically acceptable carrier.

96. A method of inhibiting the expression of HIF1 $\alpha$  and HIF2 $\alpha$  in cells or tissues comprising contacting said cells or tissues with the compound of claim 91 so that expression of HIF1 $\alpha$  and HIF2 $\alpha$  is inhibited.

97. A method of inhibiting the expression of HIF1 $\alpha$  and HIF2 $\alpha$  in cells or tissues comprising contacting said cells or tissues with (i) a first compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding HIF1 $\alpha$ , wherein said first compound specifically hybridizes with said nucleic acid molecule encoding HIF1 $\alpha$  and inhibits expression of HIF1 $\alpha$ , and (ii) a second compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding HIF2 $\alpha$ , wherein said second compound specifically hybridizes with said nucleic acid molecule encoding HIF2 $\alpha$  and inhibits expression of HIF2 $\alpha$ , so that expression of HIF1 $\alpha$  and HIF2 $\alpha$  is inhibited.

98. A method of modulating hypoxia-inducible gene expression in cells or tissues comprising contacting said cells or tissues with (i) a first compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding HIF1 $\alpha$ , wherein said first compound specifically hybridizes with said nucleic acid molecule encoding HIF1 $\alpha$  and inhibits expression of HIF1 $\alpha$ , and (ii) a second compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding HIF2 $\alpha$ , wherein said second compound specifically hybridizes with said nucleic acid molecule encoding HIF2 $\alpha$  and inhibits expression of HIF2 $\alpha$ , so that expression of HIF1 $\alpha$  and HIF2 $\alpha$  is inhibited.

99. The method of claim 98 wherein said cells or tissues are cancer cells or tissues.

100. The method of claim 99 wherein the cancer cells or tissues carry a p53 mutation.

101. A method of modulating hypoxia-inducible gene expression in cells or tissues comprising contacting said cells or tissues with a compound of claim 91 so that expression of HIF1 $\alpha$  and HIF2 $\alpha$  is inhibited.

102. The method of claim 101 wherein said cells or tissues are cancer cells or tissues.

103. The method of claim 102 wherein the cancer cells or tissues carry a p53 mutation.

104. A method of treating an animal having a disease or condition associated with hypoxia or a hypoxia-inducible factor or a hypoxia inducible gene comprising administering to said animal (i) a therapeutically or prophylactically effective amount of a first compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding HIF1 $\alpha$ , wherein said first compound specifically hybridizes with said nucleic acid molecule encoding HIF1 $\alpha$  and inhibits expression of HIF1 $\alpha$ , and (ii) a therapeutically or prophylactically effective amount of a second compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding HIF2 $\alpha$ , wherein said second compound specifically hybridizes with said nucleic acid molecule encoding HIF2 $\alpha$  and inhibits expression of HIF2 $\alpha$ , so that expression of HIF1 $\alpha$  and HIF2 $\alpha$  is inhibited.

105. The method of claim 104 wherein the disease or condition is a hyperproliferative disorder.

106. The method of claim 105 wherein the hyperproliferative disorder is cancer.

107. The method of claim 106 wherein the cancer carries a p53 mutation.

108. The method of claim 105 wherein the hyperproliferative disorder is an angiogenic disorder.

109. The method of claim 108 wherein the angiogenic disorder affects the eye.

110. A method of treating an animal having a disease or condition associated with hypoxia or a hypoxia-inducible factor or a hypoxia inducible gene comprising administering to said animal a therapeutically or prophylactically effective amount of a compound of claim 91 so that expression of HIF1 $\alpha$  and HIF2 $\alpha$  is inhibited.

111. The method of claim 110 wherein the disease or condition is a hyperproliferative disorder.

112. The method of claim 111 wherein the hyperproliferative disorder is cancer.

113. The method of claim 112 wherein the cancer carries a p53 mutation.

114. The method of claim 111 wherein the hyperproliferative disorder is an angiogenic disorder.

115. The method of claim 114 wherein the angiogenic disorder affects the eye.